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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,464	10/18/2001	William D. Huse	AME-06381	7635

23535 7590 10/30/2003

MEDLEN & CARROLL, LLP  
101 HOWARD STREET  
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SAN FRANCISCO, CA 94105

EXAMINER
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HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 10/30/2003

20

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/982,464

Applicant(s)

HUSE ET AL

Examiner

Larry R. Helms

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 11 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 19
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

1. Claims 1-2, 7-8, 13-14, 19-20 have been amended.
2. Claims 1-24 are pending and under examination.
3. The text of those sections of title 35, USC Code not included on the Office Action can be found in a prior Office Action.
4. The following Office Action contains NEW GROUNDS of rejections.

### ***Rejections Withdrawn***

5. The rejection of claims 1-24 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

### ***Response to Arguments***

6. The rejection of claims 1, 3-7, 9-13, 15-19, 21-24 under 35 U.S.C. 102(e) as being anticipated by Aruffo et al (U.S. Patent 6,312,693, filed 2/1999) is maintained.

The response filed 8/11/03 has been carefully considered but is deemed not to be persuasive. The response states that in view of the attached 131 declaration of Dr. Watkins the 102(e) and 103(a) rejections must be withdrawn. The declaration of Dr. Watkins has been carefully considered but is deemed not to be persuasive. The declaration is not signed by all of the inventors and does not state that the work was performed in the US. In addition, the declaration states that Dr. Watkins performed the work of the overlapping oligonucleotides and cites evidence in the comparison between

various pages in the application and the patent of Arruffo. In response to this argument, it is unclear what providing evidence only for the oligo work antedates the reference. In addition, it is now unclear due to the statement in the declaration that Dr. Watkins invented the oligo work what the contributions of the other two inventors, Dr. Huse and Dr. Wu were. Moreover, the declaration brings into question the contribution of the others named on the Arruffo patent. The claims are to heavy and light chains that were made by the instantly claimed method. Were any of the inventors named on the Arruffo patent also inventors on the instant claims? What are their contributions? The declaration is not persuasive and the rejection stands.

7. The rejection of claims 1-24 under 35 U.S.C. 103(a) as being unpatentable over Jones et al (Nature 321:522, 1986) and further in view of Yelton et al (The Journal of Immunology 155:1994-2004, 1995) and Soderlind et al (Gene 160:269-72, 1995) and Hagiwara et al (U.S. Patent 5,589,573, issued 12/96) is maintained.

The response filed 8/11/03 has been carefully considered but is deemed not to be persuasive. The response states that Jones does not recognize a problem of lower affinity or that the problem needs to be fixed and there is no justification to combine Jones with antibody maturation papers (see page 12 of response). In response to this argument, the Jones reference was published previous (1986, in fact 9 years prior) to the Yelton reference which teaches affinity maturation. It would have been obvious at the time of the Yelton reference to apply affinity maturation to the antibody of Jones to obtain better binding affinity for therapy and humanization as taught by Yelton.

The response further states that Yelton cautions that higher affinity may not be advantageous and Yelton cannot be offered as a reference that teaches grafting always creates a problem that needs to be solved with changes to the CDR and Yelton does not use overlapping oligos (see page 12-13 of response). In response to this argument, the Yelton reference clearly teaches advantages of affinity maturation not that there is a problem with grafting and Yelton teaches affinity improvements for single chain immunotoxins. In addition, Yelton clearly teaches that antibodies that had higher affinity performed better in therapeutic tumor models and the higher affinity antibodies had a better tumor:normal tissue ratio than lower affinity Mabs (see page 2002). Thus, taken in its whole Yelton teach there is a clear advantage to have higher affinity antibodies. The advantages of using overlapping oligos was taught by Soderlind as allowing the construction of the library in one single PCR reaction (see abstract). Thus there would be an advantage to use this technique.

The response further states that Soderlind does not attempt to retain antigen binding (see page 13 of response). In response to this argument, Soderlind was cited to provide a library of overlapping oligos with random CDRs and no framework alteration and that this technique was well known in the art and has benefit because the library can be constructed in one PCR reaction (see abstract).

The response further states that Hagiwara is not an antibody engineering reference (see page 12 of response). In response to this argument, the reference was cited to provide a teaching that visual representation in an electronic form for antibodies was well known in the art at the time of the claimed invention.

The response further states that even if (improperly) combined, all of the elements are not taught and the Examiner is requested to note step "D" of claim 1 for combining nucleic acids for frameworks with nucleic acids for modified CDR sequences and the specification teaches "The present invention combines these steps such that CDR grafting and binding reacquisition occur in a single simultaneous procedure" and in no point does Jones or Yelton teach the two procedures are to be performed in one step (see pages 13-14 of response). In response to this argument, part "D" of claim 1 requires treating overlapping oligos such that a population of altered heavy chain variable region encoding nucleic acids is constructed wherein the acceptor frameworks are unmodified with respect to the second reference. There is nothing in part "D" stating binding or a single step of CDR grafting and binding. It is unclear how one could perform in one step or simultaneously grafting of at the nucleic acid level with binding which required expression of the polypeptide and a binding assay simultaneously. Combining Jones which teaches CDR grafting and Yelton who teaches affinity maturation by altering the CDRs one would be grafting and then performing a binding step to obtain better affinity, however this is not recited in any of the claims.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

8. The rejection of claims 1-24 under 35 U.S.C. 103(a) as being unpatentable over Aruffo et al (U.S. Patent 6,312,693, filed 2/99) as applied to claims 1, 3-7, 9-13, 15-19,

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21-24 above, and further in view of Hagiwara et al (U.S. Patent 5,589,573, issued 12/96) is maintained.

The response filed 8/11/03 has been carefully considered but is deemed not to be persuasive. The response is addressed above in the 102(e) rejection of Arruffo. The same response above to the 102(e) rejection is applicable and made in this rejection.

***The following is a NEW GROUND of rejection***

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(f) he did not himself invent the subject matter sought to be patented.

10. Claims 1-24 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

Because of the declaration filed 8/13/03 by Dr. Watkins stating that he performed the work of the overlapping oligonucleotides and cites evidence in the comparison between various pages in the application and the patent of Arruffo, it is now unclear due to the statement in the declaration that Dr. Watkins invented the oligo work what the contributions of the other two inventors, Dr. Huse and Dr. Wu were. Moreover, the declaration brings into question the contribution of the others named on the Arruffo patent. The claims are to heavy and light chains that were made by the instantly claimed method. Were any of the inventors named on the Arruffo patent also inventors

on the instant claims? What are there contributions? It is requested that the contributions of all inventors and those named on the Aruffo patent be explained.

### ***Conclusion***

11. No claim is allowed.
12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703)



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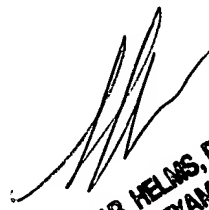
306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879



LARRY R. HELMS, PH.D.  
PRIMARY EXAMINER